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The Synthesis of 3-Spirooxindole Derivatives. VIII.[1] Total Syntheses of (±)-Formosanine, (±)-Isoformosanine, (±)-Mitraphylline and (±)-Isomitraphylline

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The total synthesis of the entitled four alkaloids, which were oxindole alkaloids of *Uncaria* species and *Mitragyna* species, has been completed through several steps starting from the condensation of 2-hydroxytryptamine hydrochloride (IV) with 3,3-dimethoxypropionaldehyde (V).

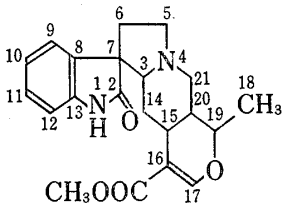
The condensation product (XV) was submitted to the Michael addition with methyl vinyl ketone, followed by acid treatment to give the α,β-unsaturated ketones (XIVa,b) as two stereoisomers. The isomer (XIVb) was condensed with methyl malonate to yield the ester (XXb), which was hydrogenated with Adams' catalyst to XXIb. The compound (XXIb) was treated with dil. sulfuric acid to give the lactones (XXIIa, b) as two spiro-isomers, the isomer (XXIIa) of which in turn, was heated with the aminal ester, then stirred with 5% MeOH–HCl, refluxed with aq. dioxane and heated with PPA to afford (±)-formosanine (IIIa) and (±)-isoformosanine (IIIb). Similarly, the lactone (XXVa) which was obtained from (XXb) by reduction with $NaBH_4$ and hydrolysis with acid, gave (±)-mitraphylline (IIa) and (±)-isomitraphylline (IIb).

The pentacyclic oxindole alkaloids which are represented by the common plane formula (I), are isolated from the tropical and subtropical plants of *Rubiaceae* family, particularly from the genera *Mitragyna* and *Ourouparia*, whose leaves have been sometimes used as traditional medicines in Africa and Asia, although there is a description that *M. speciosa* and *M. parvifolia* Korth. enjoy an undeserved reputation as a cute for opium addiction.[3]

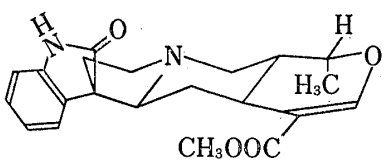
The plane formula (I) for mitraphylline and isomitraphylline was proposed by Seaton, *et al.*[4] and independently by Nozoye.[5] As for the stereochemistry of these alkaloids, Wenkert[6] presented IIa for mitraphylline and IIb for isomitraphylline, which were later confirmed by Finch and Taylor[7] and Shavel and Zinnes,[8] who converted ajmalicine of known stereochemistry to mitraphylline and isomitraphylline. Moreover, they assigned the oxindole carbonyl above the C/D ring plane for mitraphylline (IIa) and below the same plane for isomitraphylline (IIb) to establish the whole stereochemistry.[7]

On the other hand, uncarine A and uncarine B were isolated from *Uncaria kawakamii* and named by Kondo.[9,10] The identity of formosanine with uncarine B was established by

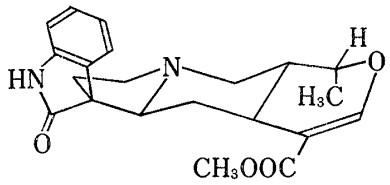
1) *a*) Part VII: Y. Ban, M. Seto, and T. Oishi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2605 (1975); *b*) Part VI: Y. Ban, N. Taga, and T. Oishi, *Tetrahedron Letters*, **1974**, 187. A portion of the present work was published as a communication in Part VI.
2) Location: *Kita 12-jo, Nishi 6-chome, Kita-ku, Sapporo, 060, Japan*; *a*) Present address: *Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., 2-2-50 Toda, Saitama-ken, 335, Japan*; *b*) Present address: *The Institute of Physical and Chemical Research, Wako-shi, Saitama-ken, 351, Japan.*
3) J.E. Saxton, "The Alkaloids, Chemistry and Physiology," Vol. VIII, edited by R.H.F. Manske, Academic Press, New York, 1965, p. 59.
4) J.C. Seaton, R. Tondeur, and L. Marion, *Can. J. Chem.*, **36**, 1031 (1958).
5) T. Nozoye, *Chem. Pharm. Bull.* (Tokyo), **6**, 306 (1958).
6) E. Wenkert, B. Wickberg, and C. Leicht, *Tetrahedron Letters*, **1961**, 822.
7) N. Finch and W.I. Taylor, *J. Am. Chem. Soc.*, **84**, 1318, 3871 (1962).
8) J. Shavel, Jr. and H. Zinnes, *J. Am. Chem. Soc.*, **84**, 1320 (1962).
9) H. Kondo and T. Ikeda, *J. Pharm. Soc. Japan*, **61**, 416, 453 (1941).
10) H. Kondo, T. Nozoye, and M. Tomita, *Ann. Rept. Itsuu Lab.*, **4**, 77 (1953).



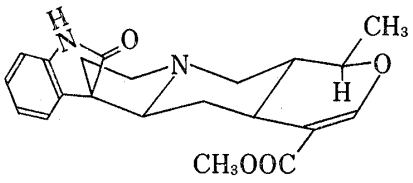
I[a)]



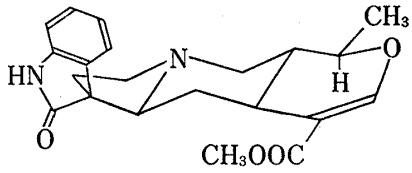
mitraphylline (IIa)



isomitraphylline (IIb)



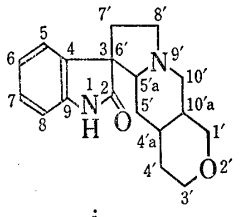
formosanine (IIIa)



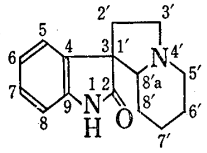
isoformosanine (IIIb)

Chart 1

a) The trivial names in this Chart and numbering system shown in formula (I) are adopted for the natural alkaloids. The numbering systems for the pentacyclic and tetracyclic oxindole derivatives in the present syntheses are demonstrated as (i) and (ii), respectively.



i



ii

Raymond-Hamet[11] who had isolated the alkaloid from *Ourouparia formosana*, and given the name "formosanine" to this alkaloid.[12] The identity of isoformosanine with uncarine A was also established.[13] The study of the 100 MHz nuclear magnetic resonance (NMR) spectrum of formosanine was carried out by Beecham[14] and by Shamma,[13] who showed the *pseudo trans-diaxial* configuration for the C-19-H and C-20-H arrangement [Found: J_{19-20}= 9 Hz. Calcd. J_{19-20}=10 Hz (Φ=165°)][13] which is demonstrated by formula (IIIa). The close similarity of the CD spectra of formosanine to that of mitraphylline (IIa) is compatible with the above assignment of *trans*-D/E ring junction.[14] Therefore, formosanine (IIIa) and isoformosanine (IIIb) are the C-19 epimers of mitraphylline (IIa) and isomitraphylline (IIb), respectively. The conclusion is in good agreement with the result on comparison of pK_a values, and with the observation that the signal of the *pseudo-axial* C-19-H (δ 3.76) of formosanine is present in the higher magnetic field, due to the shielding effect of the double bond at C-16 and C-17, than the corresponding signals (δ 4.34 and δ 4.39) of mitraphylline (IIa) and isomitraphylline (IIb), respectively.[13,14] Their relationship as a pair of stereoisomers at 3-spiro position is shown by their ready interconversion and equilibration with acid and base.[3]

A stereoselective total synthesis of (±)-formosanine [IIIa, (±)-uncarine B] and (±)-isoformosanine [IIIb, (±)-uncarine A] was achieved by Winterfeldt according to an oxidative conversion of 3-iso-19-epi-ajmalicine (v) at the final step, which method had been developed

11) *a*) Raymond-Hamet, *Compt. Rend.*, **245**, 1458 (1957); *b*) J.C. Seaton, M.D. Nair, O.E. Edwards, and L. Marion, *Can. J. Chem.*, **38**, 1035 (1960).
12) *a*) Raymond-Hamet, *Compt. Rend.*, **203**, 1383 (1936); *b*) Raymond-Hamet, *Bull. Soc. Chim. France*, **10**, 129 (1943).
13) M. Shamma, R.J. Shine, I. Kompis, T. Sticzay, F. Morsingh, J. Poisson, and J.-L. Pousset, *J. Am. Chem. Soc.*, **89**, 1739 (1967).
14) *a*) A.F. Beecham, N.K. Hart, S.R. Johns, and J.A. Lamberton, *Chem. Commun.*, **535** (1967); *b*) A.F. Beecham, N.K. Hart, S.R. Johns, and J.A. Lamberton, *Australian J. Chem.*, **21**, 491 (1968).

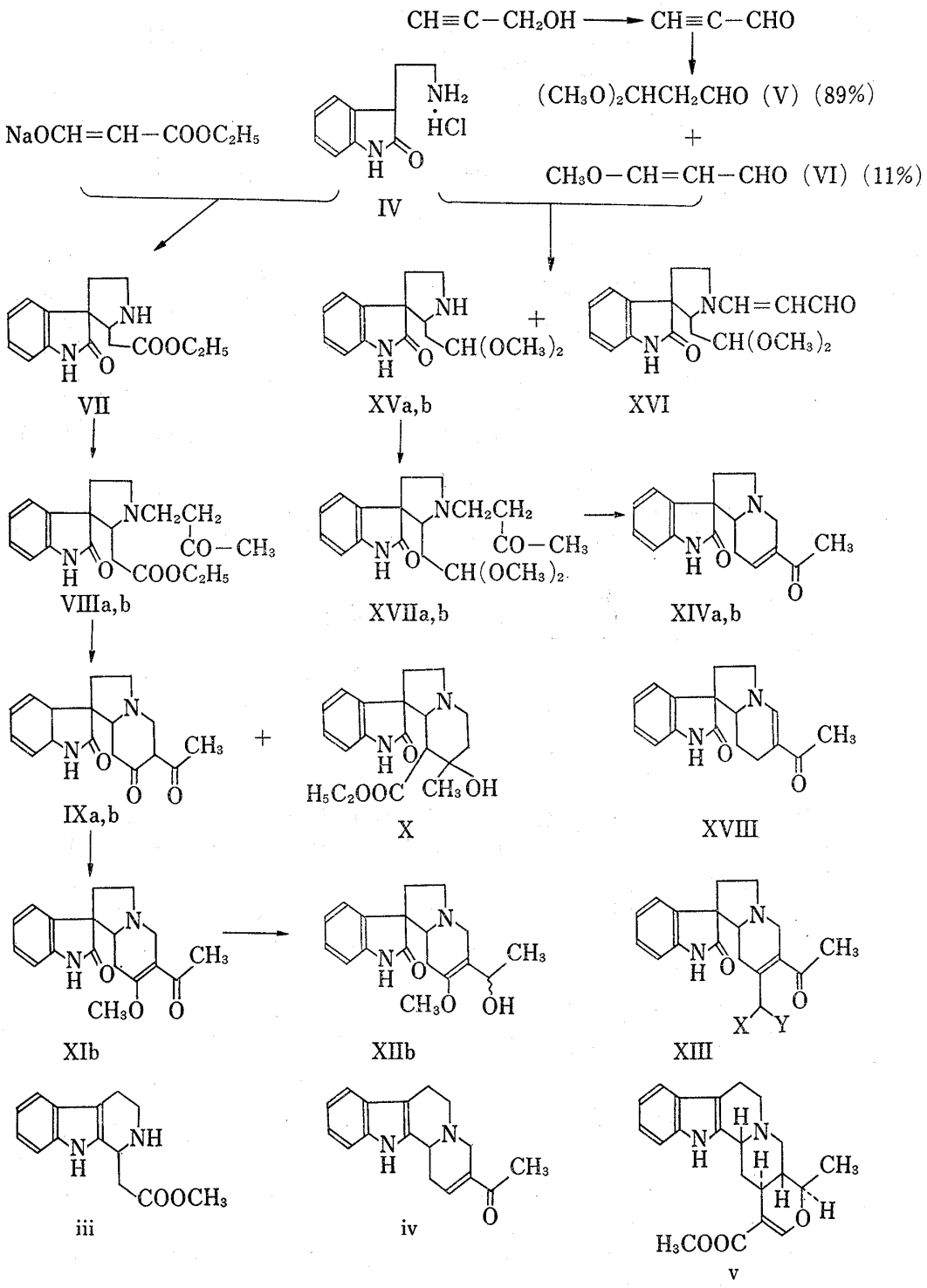


Chart 2

by Shavel[8] and by Finch,[7] independently, for the conversion of indole to oxindole.[15a] A new stereoselective total synthesis of (±)-formosanine (IIIa), (±)-isoformosanine (IIIb), (±)-mitraphylline (IIa) and (±)-isomitraphylline (IIb) is described in this publication, and the feature of the present synthesis is to have started from the condensation of 2-hydroxytry-

15) *a*) E. Winterfeldt, A.J. Gaskell, T. Korth, H.-E. Radunz, and M. Walkowiak, *Chem. Ber.*, **102**, 3558 (1969); *b*) The latest publication by E. Winterfeldt school: G. Benz, H. Riesner, and E. Winterfeldt, *ibid.*, **108**, 248 (1975). References cited therein.

ptamine hydrochloride (IV) with 3,3-dimethoxypropionaldehyde (V) in reference to our synthesis of (±)-rhynchophylline and (±)-isorhynchophylline.[1a] Therefore, the present paper describes various oxindole derivatives which have not been known, although the corresponding indole derivatives have been so far well investigated.[15]

Prior to the successful experiments, we attempted to make use of the compound (VII) which was proficiently prepared in this laboratory,[1a] as the corresponding indole derivative (iii)[16] was employed by Winterfeldt as a starting material for the above synthesis through (iv) and (v).

Thus, the ester (VII) was condensed with methyl vinyl ketone in benzene at room termperature to give the compound (VIII)[17] as a pale yellow oil in 94% yield. As the product (VIII) indicated two spots on thin-layer chromatography (TLC), it may be assumed to be a mixture of the spiroisomers (VIIIa, b), but on chromatography the starting material (VII) was reproduced as a result of the retro-Michael reaction of the product. Therefore, the crude product (VIIIa, b) was submitted to the Dieckmann condensation with sodium ethoxide in toluene at room temperature to afford the diketone as two isomers, (IXa, mp 177—178°, 10% yield) and (IXb, mp 182°, 50% yield).[17] The assignment of these structures was mainly due to the disappearance of the proton signals ($OC\underline{H}_2C\underline{H}_3$) due to the ethyl ester absorptions in NMR, the peak at *m/e* 298 (M^+) in the mass spectroscopy, and the infrared (IR) spectra indicating the Bohlmann's absorptions of *trans*-indolizidine.[18] At the same time, the compound [X, *m/e* 344 (M^+)] was obtained as a by-product in 16% yield. The product (IXa) was treated with a base to afford IXb, and IXb was heated with an acid to furnish IXa, suggesting that with the former (IXa) the oxindole carbonyl is above the C/D ring plane and with the latter (IXb), *vice versa*.

The differentiation of the reactivities of two keto groups in IXa,b was investigated by the attempt to make the hydrazone, thioketal and reduction products, but no selectivity was found at all. Finally, IXb was reacted with diazomethane in ether–methanol to give the keto enol-ether (XIb) though in a low yield. To determine the direction of enolization, the compound (XIb) was reduced with $NaBH_4$ to give the alcoholic enol-ether (XIIb), whose NMR indicated two doublets at δ 1.24 and 1.26 (J=7 Hz) instead of the signal at δ 2.38 (3H, s, $CO\text{-}C\underline{H}_3$) of the keto enol-ether (XIb). Accordingly, the reduction product (XII) should be a mixture of diastereoisomers with the different configuration of hydroxyl groups. Thus, the structure of the keto enol-ether should be XIb, in which the orientation of the double bond due to enolization should be located between C-6′ and C-7′. The Michael condensation of XIb with the compounds involving the active methylene groups ($CH_2\langle^{X}_{Y}$: X, Y=CO_2Me, CO_2Et, CO_2Bu^t, and CN *etc.*) were tried many times under various conditions, but any objective compound (XIII) was not obtained. As the methoxyl substituent at C-7′ may be assumed to give a deactivating effect to the receptor (XIb), the synthesis of the unsaturated ketone (XIV) was attempted with success in the following way.

3,3-Dimethoxypropionaldehyde [V, bp_7 40—41°] was prepared as a starting material by addition of methanol to propiol aldehyde,[19] which was obtained by oxidation of propargyl alcohol with chromium trioxide.[20] The compound (V) was proved to be contaminated with 11% of 3-methoxyacrolein (VI) based upon the NMR spectrum. A solution of 2-hydroxytry-

16) *a*) G.B. Kline, *J. Am. Chem. Soc.*, **81**, 2251 (1959); *b*) L.H. Groves and G.A. Swan, *J. Chem. Soc.*, **1952**, 650.
17) The compounds (VIII and IX) were first prepared by Dr. Masahiko Seto in this laboratory. We acknowledge his cooperation for providing these procedures.
18) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
19) A.K. Skoldinow, A.P. Arendank, and T.M. Godzhello, *J. Org. Chem. USSR*, **6**, 421 (1970).
20) F. Wille, L. Saffer, and W. Weisskopf, *Ann.*, **568**, 34 (1950). *cf.*) J.C. Sauer, "Organic Syntheses," Coll. Vol. 4, John Wiley & Sons, Inc., New York, 1963, p. 813.

ptamine hydrochloride (IV) and V of the above purity in aqueous methanol containing NaOH was allowed to stand at room temperature for 2 days to give acetal (XV) in 72% yield along with XVI as a by-product in 16% yield. The main product (XV) indicated one spot on TLC, though its NMR spectrum indicated two pairs of methyl proton signals of methoxyl group, which suggested that the compound (XV) might consist of two spiroisomers. The by-product (XVI) must have been generated by Michael condensation of the main product (XV) with 3-methoxyacrolein, followed by elimination of methanol. Separation of two products, however, was very easy because the latter (XVI) is almost insoluble in various organic solvents. The compound (XV) was condensed with methyl vinyl ketone in dry benzene at room temperature overnight to provide the keto acetal (XVII) in 90% yield as a pale yellow resin, which was shown to be a mixture of two 3-spiro isomers by two spots on TLC and two pairs of methyl proton signals. Subsequently, the crude product (XVII) without purification was treated with 10% HCl–AcOH (1:1) at 100° for 2 hr to give the α,β-unsaturated ketone as two 3-spiroisomers, (XIVa, mp 171°, 65% yield from XV) and (XIVb, mp 144—145°, 31% yield from XV), after separation by silica gel chromatography. Either of these isomers lacked the absorption around 300 nm, which excluded the possibility of the enamide isomer (XVIII).

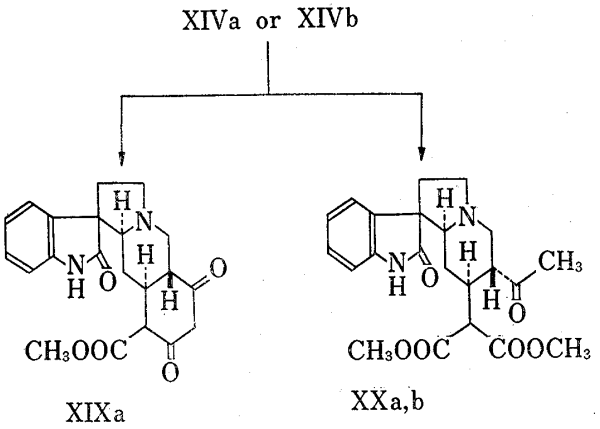


Chart 3

The Michael condensation of XIVa with dimethyl malonate in methanol containing 1.1 mol. equiv. of NaOMe gave the diketoester (XIXa, mp 203—204°) in high yield as a result of the progress of the favorable reaction which was immediately followed by the intramolecular Claisen condensation. The structure of this compound (XIXa) was assigned mainly due to the mass spectrum [*m/e*: 382 (M^+)] and the methyl proton signal (3H, s) at δ: 3.30 in the NMR spectrum. Therefore, XIVa was treated with a less amount of NaOMe (0.5 mol. equiv.) to afford the objective compound (XXa, mp 204—205°) in 78% yield. Similarly, XIVb gave XXb, mp 171°, in 57% yield, in which the substituents at C-6′ and C-7′ should be thermodynamically stable *trans-diequatorial*. Moreover, both compounds (XXa, b) may be assumed to involve the *trans*-indolizidine based on the Bohlmann's strong absorptions at 2800 cm^{-1} in their infrared spectra.[18] The same products [XXa, mp 197°, and XXb, oil] were obtained by Winterfeldt[21] through oxidative rearrangement of the corresponding indole with *t*-butyl hypochlorite, followed by treatment with MeOH–KOH, but the present products might be of higher purity.

The compound (XXb) was hydrogenated with Adams' catalyst in methanol to give the hydroxy-diester [XXIb, mp 181—182° (decomp.), *m/e*: 416 (M^+); NMR ($CDCl_3$) δ: 1.21 (3H, d, $-CH(OH)-C\underline{H}_3$), 3.60 (3H, s, $OC\underline{H}_3$) and 3.68 (3H, s, $OC\underline{H}_3$); *ca.* 100% yield], which was refluxed with dil. H_2SO_4 in AcOH to afford the two isomeric lactones, [XXIIb, mp 269° (decomp.), 32% yield] and [XXIIa, mp 268° (decomp.), 41% yield]. Even on treatment of XXIb with dil. HCl at room temperature, however, the generation of the lactone (XXIII) was not recognized. Both of the products (XXIIa, b) indicated the peaks [*m/e*: 326 (M^+)] in the mass spectra and the proton signals at δ: 1.24 (3H, d, C-1′-$C\underline{H}_3$) and δ: 4.10—4.14 (1H, m, C-1′-$\underline{H}$) in the NMR spectra. The multiplet of C-1′-H signal was collapsed to a doublet ($J_{1'-10'a}$=8 Hz) on irradiation at the C-1′-$C\underline{H}_3$ frequency, which demonstrated that the configuration at C-1′-H and C-10′a-H should be *trans-diaxial*. On reduction of XXb with $NaBH_4$ in methanol at −5——10°

21) A.J. Gaskell, H.-E. Radunz, and E. Winterfeldt, *Tetrahedron*, **26**, 5353 (1970).

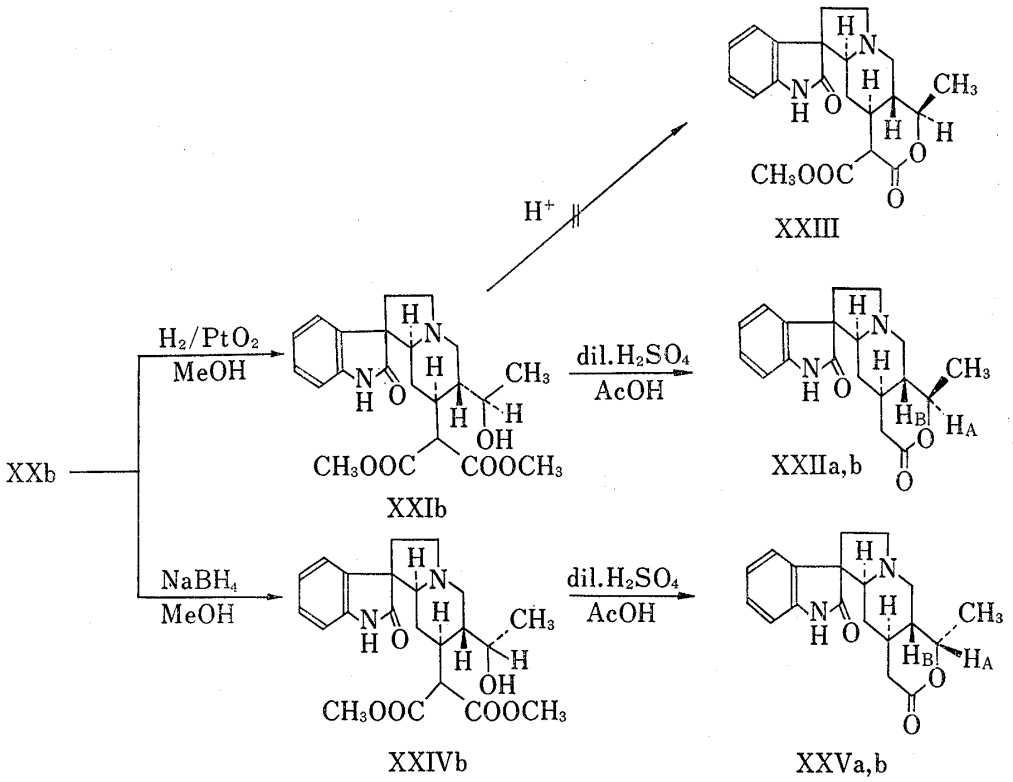


Chart 4

was obtained XXIVb [mp 180—181° (decomp.), *m/e*: 416 (M^+), NMR ($CDCl_3$) δ: 1.23 (3H, d, C-1′-C$\underline{H}_3$), 3.61 (3H, s, OC$\underline{H}_3$), and 3.69 (3H, s, OC$\underline{H}_3$); 87% yield] as a sole product, which was heated with dil. H_2SO_4 in AcOH in a similar manner to give the two isomeric lactones, (XXVb, mp 258°, 29% yield) and (XXVa, mp 254°, 56% yield). Both of the products (XXVa, b) indicated the peaks [*m/e*: 326 (M^+)] in the mass spectra and the proton signals at δ: 1.18 (3H, d, C-1′-C$\underline{H}_3$) and 4.60 (1H, m, C-1′-$\underline{H}$) in the NMR spectra. The coupling constant ($J_{1'-10'a}$= 4 Hz) which was obtained by decoupling technique, revealed the *cis*-relationship between C-1′-H and C-10′a-H to be *equatorial-axial*. The result of these remarkable stereoselectivities is noteworthy and could be considered to be a result of the steric approach control of hydrogen or hydride to the substrate, which mechanism should be similar to that proposed by Winterfeldt for analogous reactions of indole derivatives.[15a)]

It was readily conceivable that formylation of the lactones (XXII and XXV), followed by acyl-lactone rearrangement[22)] and methylation should afford the objective alkaloids. Inasmuch as either of the above lactones is insoluble in inert solvents such as benzene, tetrahydrofuran, and 1,2-dimethoxyethane *etc.*, it was anticipated that ethyl formate could not be employed as a formylating agent. Thus, the lactone (XXIIa) was heated with bis(dimethylamino)-*tert.* butyloxymethane[aminal *t*-butylester, $(Me_2N)_2CH$–O–*tert.*Bu][23)] in dimethylformamide at 50° for 1 hr and at 100° for further 1 hr to afford the vinylogous carbamate {XXVIa, *m/e*: 381 (M^+), UV λ_{max}^{MeOH}: 302 nm, NMR (d_6-DMSO) δ: 3.30 [6H, s, N ($C\underline{H}_3)_2$]} in 72% yield.

Subsequently, the compound (XXVIa) was heated with dilute hydrochloric acid with the aim to obtain the corresponding aldehyde which could be simultaneously subject to acyl-lactone rearrangement under the above acidic condition. After concentration of the solution, the crude product was refluxed in 5% hydrochloric acid in MeOH for 3 hr to afford the acetal

22) F. Korte and K.H. Büchel, *Angew. Chem.*, **71**, 709 (1959).
23) H. Bredereck, G. Simchen, S. Rebsdat, W. Kantlehner, P. Horn, R. Wahl, H. Hoffmann, and P. Grieshaber, *Chem. Ber.*, **101**, 41 (1968).

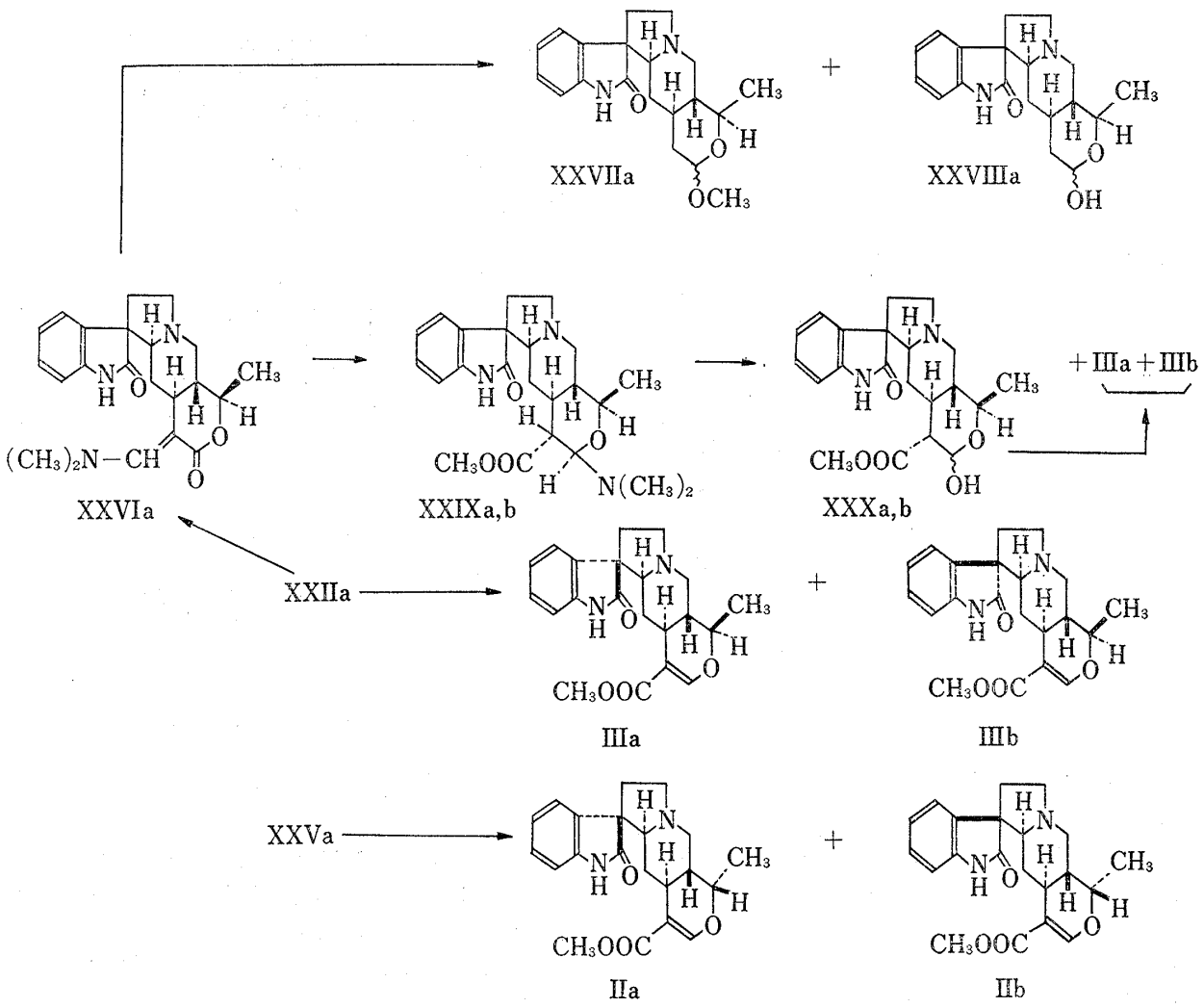


Chart 5

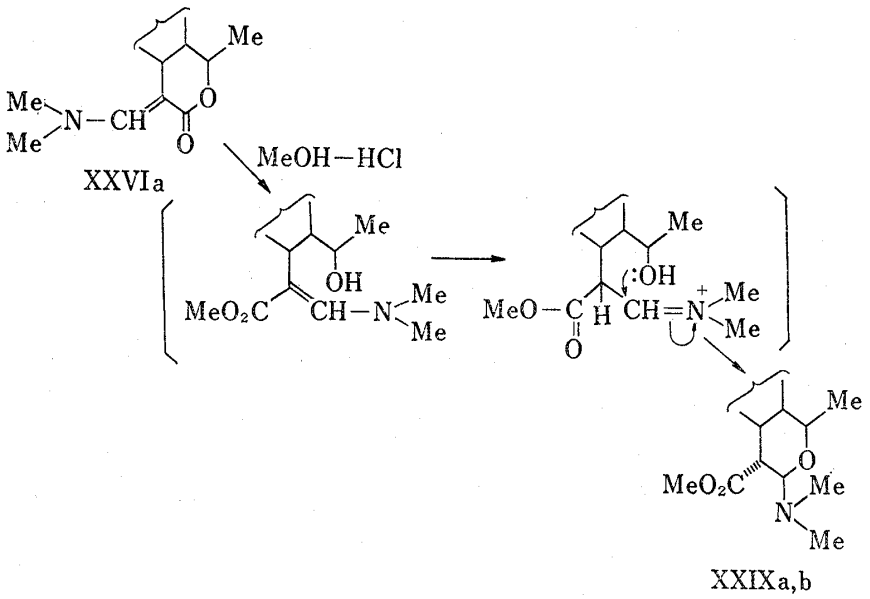


Chart 6

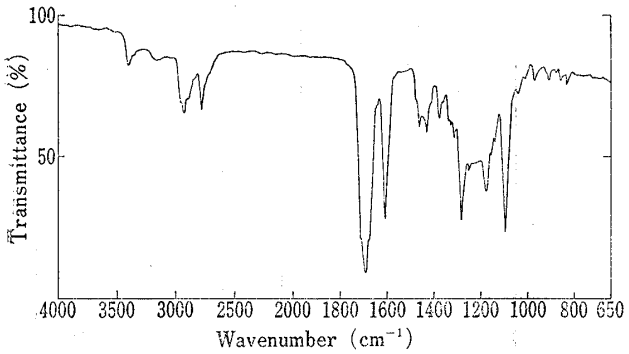


Fig. 1. IR Spectrum (in $CHCl_3$) of Synthetic (±)-Formosanine (Uncarine B)

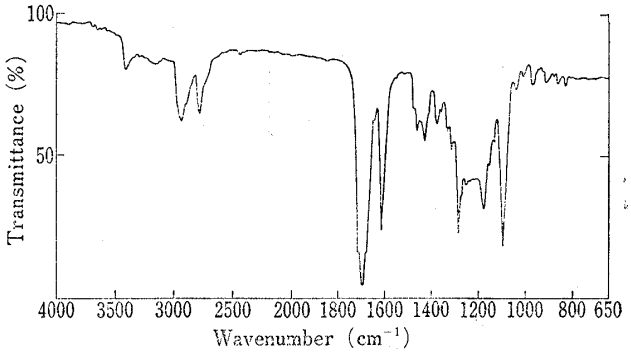


Fig. 2. IR Spectrum (in $CHCl_3$) of Natural Formosanine (Uncarine B)

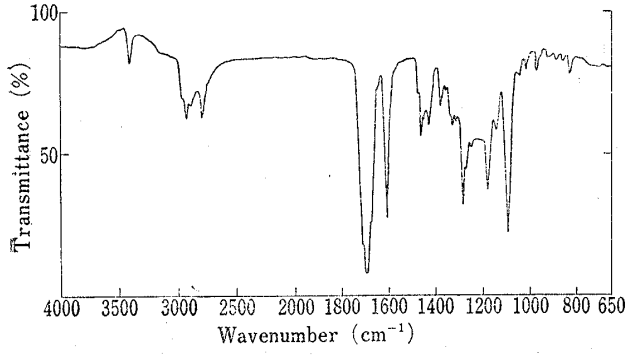


Fig. 3. IR Spectrum (in $CHCl_3$) of Synthetic (±)-Isoformosanine (Uncarine A)

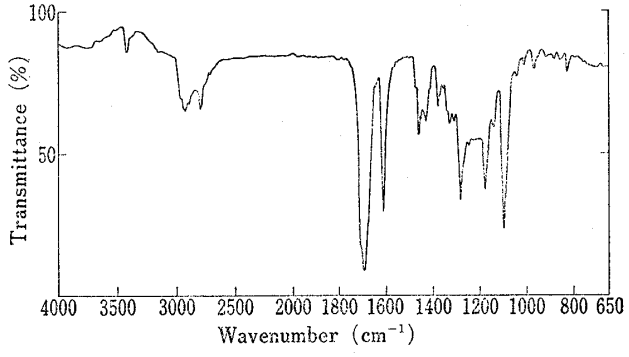


Fig. 4. IR Spectrum (in $CHCl_3$) of Natural Isoformosanine (Uncarine A)

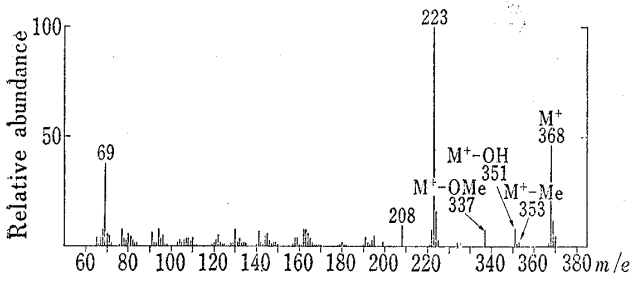


Fig. 5. Mass Spectrum of Synthetic (±)-Formosanine

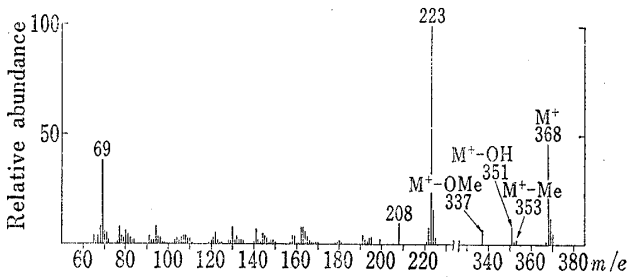


Fig. 6. Mass Spectrum of Natural Formosanine

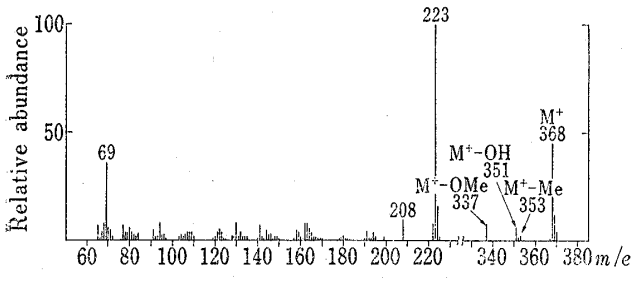


Fig. 7. Mass Spectrum of Synthetic (±)-Isoformosanine

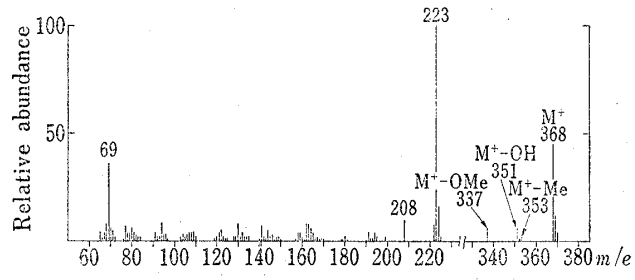


Fig. 8. Mass Spectrum of Natural Isoformosanine

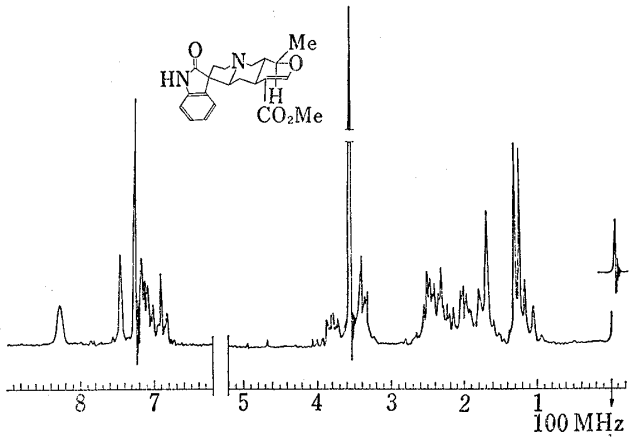


Fig. 9. NMR Spectrum (in $CDCl_3$) of Synthetic (±)-Formosanine

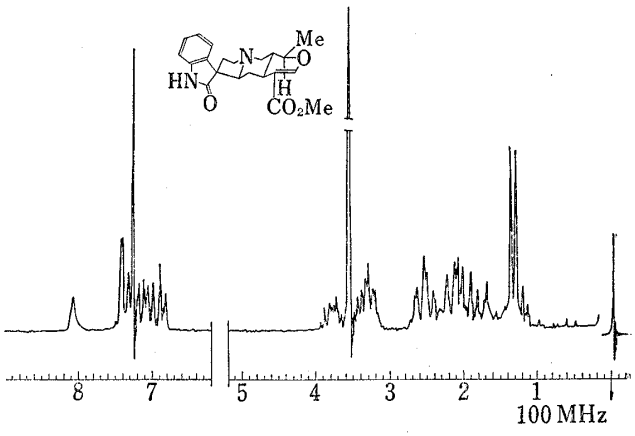


Fig. 10. NMR Spectrum (in $CDCl_3$) of Synthetic (±)-Isoformosanine

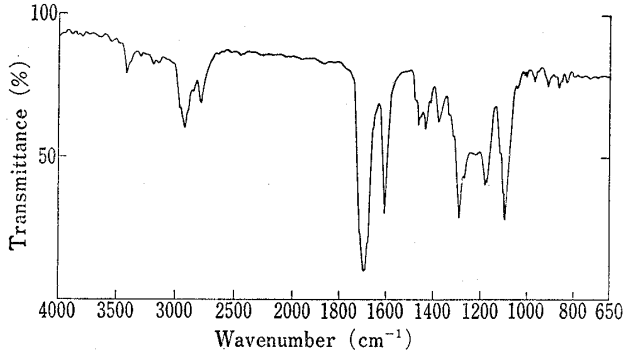


Fig. 11. IR Spectrum (in $CHCl_3$) of Synthetic (±)-Mitraphylline

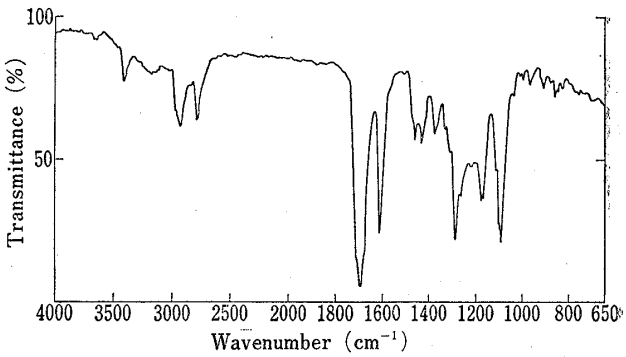


Fig. 12. IR Spectrum (in $CHCl_3$) of Natural Mitraphylline

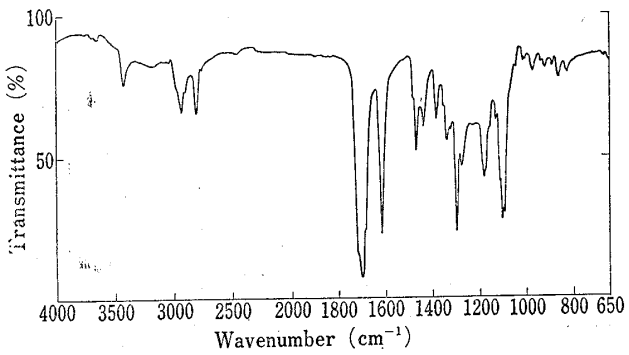


Fig. 13. IR Spectrum (in $CHCl_3$) of Synthetic (±)-Isomitraphylline

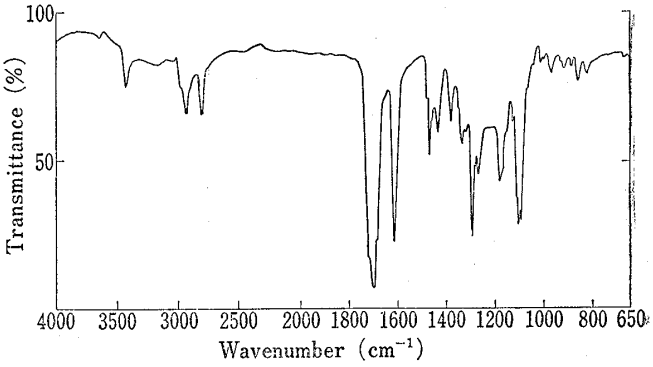


Fig. 14. IR Spectrum (in $CHCl_3$) of Natural Isomitraphylline

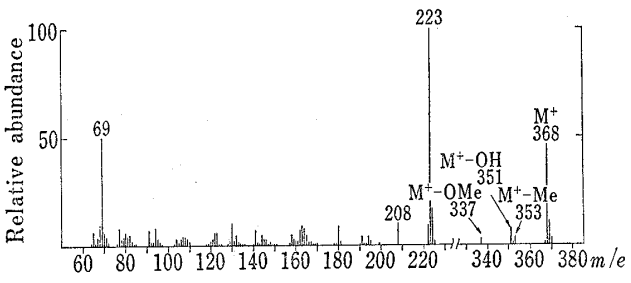


Fig. 15. Mass Spectrum of Synthetic (±)-Mitraphylline

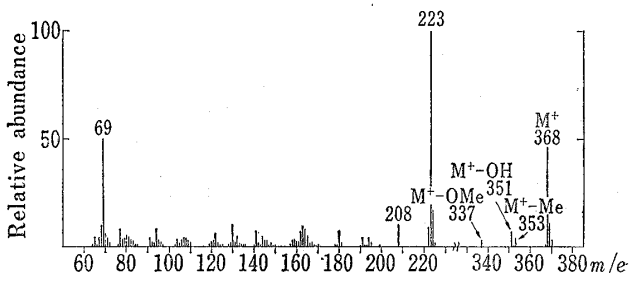


Fig. 16. Mass Spectrum of Natural Mitraphylline

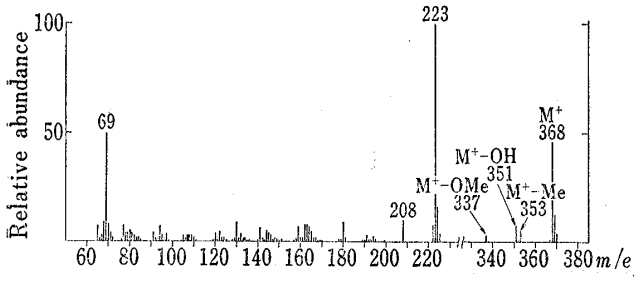


Fig. 17. Mass Spectrum of Synthetic (±)-Isomitraphylline

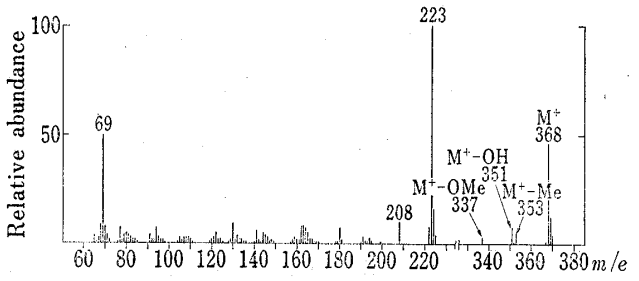


Fig. 18. Mass Spectrum of Natural Isomitraphylline

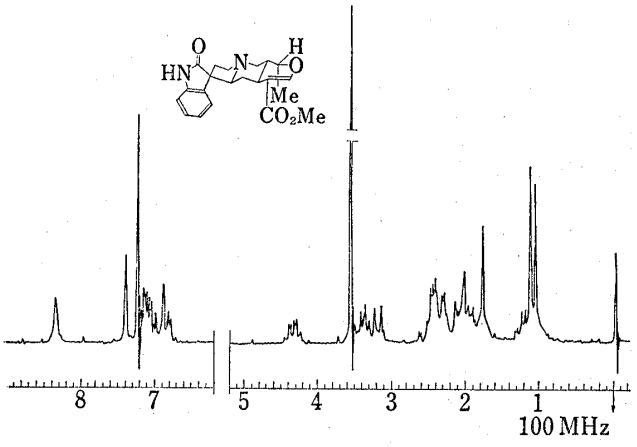


Fig. 19. NMR Spectrum (in $CDCl_3$) of Synthetic (±)-Mitraphylline

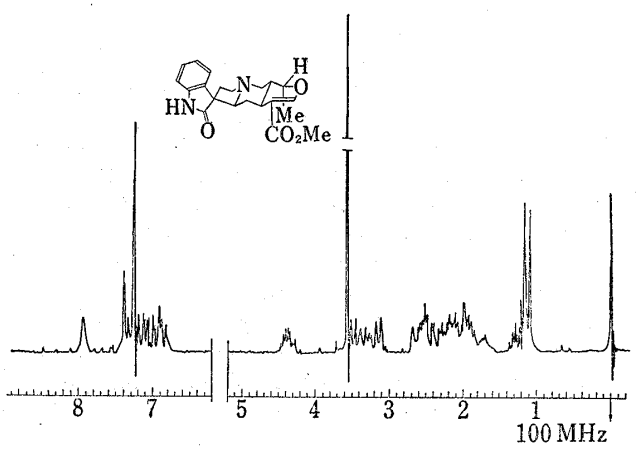


Fig. 20. NMR Spectrum (in $CDCl_3$) of Synthetic (±)-Isomitraphylline

(XXVIIa) as the main product in 79% yield along with the hemiacetal (XXVIIIa) as a minor product. Thus, it was borne out that an unfavorable reaction accompanied by decarboxylation was predominant on heating XXVIa in an aqueous acidic solution. Therefore, the compound (XXVIa) was refluxed with 5% anhydrous methanolic HCl for 5 hr to give the aminoester [XXIX, *m/e*: 413 (M^+)] in two isomeric forms, (XXIXa, mp 228°, 80% yield) and (XXIXb, mp 223—224°, 1.4% yield). The mechanism of this reaction could be shown in Chart 6.

Since the orientation of the dimethylamino-substituent at C-3′ might be assumed to be *equatorial*, a rather vigorous condition seemed to be inevitable for hydrolysis. Thus, the dihydrochloride of XXIXa was heated at reflux in aqueous dioxane for 20 hr to give the hemiacetal [XXX, *m/e*: 386 (M^+)] in two isomeric forms, (XXXa, 36% yield) and (XXXb, 22% yield). In addition to the above products, (±)-formosanine (IIIa) and (±)-isoformosanine (IIIb) were obtained in 14% and 13% yields, respectively, after chromatography on silica gel. Furthermore, when the former product (XXXa) was heated with polyphosphoric acid in 1,2-dimethoxyethane at 70° for 2 hr, (±)-formosanine (IIIa) was generated in a quantative yield. Accordingly, these processes and operations were continuously in one vessel without isolation of any intermediate to stereoselectively afford (±)-formosanine (IIIa, mp 235—236°, 35% yield from XXIIa) and (±)-isoformosanine (IIIb, 225—226°, 19% yield from XXIIa), both [*m/e*: 368 (M^+)] of which were identified with the authentic specimens of the natural alkaloids on direct comparisons of the IR ($CHCl_3$) and mass spectra, and *Rf* values on TLC, respectively. These spectral data are shown in Fig. 1—10 with the NMR spectra of the synthetic alkaloids.

Similarly, the lactone (XXVa) furnished (±)-mitraphylline (IIa, mp 242°, 27% yield) and (±)-isomitraphylline (IIb, mp 222—223°, 16% yield), which [*m/e*: 368 (M^+)] were identical

with the natural alkaloids, respectively, on comparisons of the IR ($CHCl_3$), mass spectra and *Rf* values on TLC. (See Fig. 11—20).

The total stereoselective synthesis of the entitled alkaloids has been finished through oxindole intermediates starting from 2-hydroxytryptamine. The biosynthetic aspects of the present processes will be discussed in the forthcoming paper.

Experimental[24,25]

1′-(3-Oxobutyl)-2′-ethoxycarbonylmethyl Spiro[indoline-3,3′-pyrrolidine]-2-one (VIIIa,b)——To a solution of the aminoester [VII, 10.9 g (40 mmoles)] in anhydrous benzene (250 ml) was added methyl vinyl ketone [4.6 g (66 mmoles)] with stirring under ice cooling. After the completion of addition, the whole mixture was stirred at room temperature for 20 hr. The solution was concentrated *in vacuo* to leave 12.9 g (93.5%) of the addition product (VIII) as a pale yellow oil, which indicated two spots on TLC, demonstrating the product to be a mixture of two 3-spiroisomers (VIIIa and VIIIb). On chromatography, it was reconverted to the initial compound (VII) as a result of the retro-Michael reaction, and the crude product was submitted to the subsequent reaction without any purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1720, 1700. NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 2.12 (3H, s, $COC\underline{H}_3$), 3.75 (2H, q, J=7 Hz, $-C\underline{H}_2CH_3$), 6.70—7.27 (4H, m, aromatic protons), 9.90 (1H, b-s, N$\underline{H}$). Mass Spectrum *m/e*: 274 (M^+-70), corresponding to the molecular weight of VII by the retro-Michael reaction, instead of the molecular ion peak [$C_{19}H_{24}O_4N_2$=344.40].

6′-Acetyl-7′-oxo Spiro[indoline-3,1′-indolizidine]-2-one (IXa,b) and 7′-Hydroxy-7′-methyl-8′-ethoxycarbonyl Spiro[indoline-3,1′-indolizidine]-2-one (X)[26]——To a suspension of sodium ethoxide [0.41 g (6 mmoles)] in anhydrous toluene (10 ml) was added with stirring a solution of the foregoing keto ester [VIIIa, b, 1.03 g (3 mmoles)] in anhydrous toluene (5 ml) in an ice bath over a period of 15 min. The whole mixture was stirred for an additional 30 min and then at room temperature for 17 hr, during which time sodium ethoxide was dissolved and in 2—3 hr the colorless precipitate deposited. The reaction mixture was cooled with ice, to which was added ice-water. The aqueous phase was separated, extracted with ether, acidified with acetic acid, and then made alkaline with ammonia. The solution was extracted with dichloromethane, the extract was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel. The first fraction eluted with ethyl acetate–chloroform (4: 1) afforded 442 mg (49.4%) of the diketone (IXb), which was recrystallized from ethyl acetate to give colorless needles, mp 182° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3160, 1700, 1620, 1600. NMR ($CDCl_3$) δ: 2.10 (3H, s, $COC\underline{H}_3$), 6.79—7.40 (4H, m, aromatic protons), 9.04 (1H, b-s, N$\underline{H}$). Mass Spectrum *m/e*: 298 (M^+), 255, 160, 153 (base peak). *Anal.* Calcd. for $C_{17}H_{18}O_3N_2$ (298.33): C, 68.44; H, 6.08; N, 9.38. Found: C, 68.21; H, 6.06; N, 9.20. The second fraction gave 85 mg (9.5%) of the other diketone (IXa), which was recrystallized from ethyl acetate to furnish the pure material, colorless needles, mp 177—178° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3160, 1720, 1695, 1620 and 1600 (sh). NMR ($CDCl_3$) δ: 2.10 (3H, s, $COC\underline{H}_3$), 6.80—7.35 (4H, m, aromatic protons), 9.17 (1H, b—s, N$\underline{H}$). Mass Spectrum *m/e*: 298 (M^+), 255, 160, 153 (base peak). *Anal.* Calcd. for $C_{17}H_{18}O_3N_2$ (298.33): C, 68.44; H, 6.08; N, 9.38. Found: C, 68.45; H, 6.12; N, 9.32. The third fraction gave 167 mg (16.2%) of the hydroxy-ester (X), which was recrystallized from ethyl acetate to furnish the pure material, colorless needles, mp 159—160°. IR ν_{max}^{Nujol} cm^{-1}: 3370, 3270, 1715, 1690, 1620. NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.09 (3H, s, $-C\underline{H}_3$), 3.75 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.82—7.52 (4H, m, aromatic protons), 9.28 (1H, s, N$\underline{H}$). Mass Spectrum *m/e*: 344 (M^+), 326, 298, 256, 199, 181 (base peak). *Anal.* Calcd. for $C_{19}H_{24}O_4N_2$ (344.40): C, 66.26; H, 7.02; N, 8.13. Found: C, 66.45; H, 6.94; N, 8.29.

6′-Acetyl-7′-methoxy-1′,2′,3′,5′,8′,8′a-hexahydro Spiro[indoline-3,1′-indolizine]-2-one (XIb)——To a solution of the diketone[IXb, 300 mg (1 mmole)] in methanol (25 ml) was added the ethereal solution of diazomethane (10 mol. eq.) in an ice bath. The whole solution was allowed to stand at room temperature overnight. The solution was concentrated *in vacuo* to leave the residue, which was chromatographed over silica gel. The first fraction eluted with a mixed solvent of ethyl acetate–chloroform (4: 1) afforded 105 mg of the starting material. The second fraction furnished 110 mg (35.3%) of the keto-enol-ether (XIb), which was recrystallized from ethyl acetate to give the analytically pure material, pale yellow needles, mp 180—181° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3130, 1700, 1630, 1610 (sh), 1605. NMR ($CDCl_3$) δ: 2.38 (3H, s, $COC\underline{H}_3$), 3.55

24) Melting points were measured with a hot stage microscope (Yanaco MP-J2) and uncorrected. Spectra reported herein were measured on a Hitachi EPS-3T spectrophotometer, JASCO DS-701G and 215 Hitachi grating infrared spectrophotometers, a Hitachi R-20B (NMR, 60 MHz), and a Hitachi RMU-7M double forcussing mass spectrometer. The authors are indebted to Misses H. Kakizaki, M. Satoh, A. Maeda, and C. Ohara for microanalysis, to Mmes. M. Ohnuma and K. Tsuta, and Miss S. Okayama for obtaining NMR spectra and to Miss M. Takahashi for mass spectral measurements.

25) The following abbreviations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet t=triplet. DMSO=dimethyl sulfoxide.

26) All of the indolizidine derivatives should be *trans* at the ring juncture as are mentioned in the text.

(3H, s, $OC\underline{H}_3$), 6.85—7.50 (4H, m, aromatic protons), 8.87 (1H, s, N<u>H</u>). Mass Spectrum *m/e*: 312 (M^+), 297, 167, 160, 152. *Anal.* Calcd. for $C_{18}H_{20}O_3N_2$ (312.37): C, 69.21; H, 6.45; N, 8.97. Found: C, 69.08; H. 6.50; N, 8.88.

6′-(1-Hydroxyethyl)-7′-methoxy-1′,2′,3′,5′,8′,8′a-hexahydro Spiro[indoline-3,1′-indolizine]-2-one (XIIb)—To a solution of the keto-enol-ether[XIb, 50 mg (0.16 mmole)] in methanol (4 ml) was added 100 mg of $NaBH_4$ in small portions under ice-cooling. The whole mixture was stirred at room temperature overnight, and the solution was concentrated *in vacuo* to give the residue, to which water was added. The whole solution was extracted with dichloromethane, the extract was dried over Na_2SO_4, and evaporated *in vacuo*. The crude residue was chromatographed over silica gel. Elution with ethyl acetate–methanol (9: 1) gave 35 mg (70%) of the alcoholic enol-ether (XIIb), which was recrystallized from ethyl acetate to furnish the pure material, colorless needles, mp 181° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3500—3200, 3140, 1700, 1615. NMR ($CDCl_3$) δ: 1.24 (d, J=7 Hz, >CH–C<u>H</u>$_3$), 1.26 (d, J=7 Hz, >CH–C<u>H</u>$_3$), 3.35 (3H, s, $OC\underline{H}_3$), 4.80 (1H, q, J=7 Hz, >C<u>H</u>–CH$_3$), 6.85—7.55 (4H, m, aromatic protons), 9.13 (1H, s, N<u>H</u>). Mass Spectrum *m/e*: 314 (M^+), 313, 296, 282, 160.

2′-(2,2-Dimethoxyethyl) Spiro[indoline-3,3′-pyrrolidine]-2-one(XVa,b) and 1′-(3-Oxopropenyl)-2′-(2,2-dimethoxyethyl) Spiro[indoline-3,3′-pyrrolidine]-2-one (XVI)——To a solution of 2-hydroxytryptamine hydrochloride [IV, 40.8 g, (0.192 mole)] in methanol (206 ml) and water (124 ml) was added 2 N-sodium hydroxide solution [124 ml (0.24 mole)] under ice-cooling. After the completion of addition, a solution of 3,3-dimethoxypropionaldehyde [V, 27.1 g (0.23 mole)] in methanol (206 ml) was added to the reaction mixture and the whole was allowed to stand at room temperature for 40 hr. The solution was concentrated *in vacuo* to leave the residue, which was diluted with water and extracted with dichloromethane. The extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The dark residue was chromatographed on alumina in a short column. The fraction eluted with dichloromethane–methanol (50: 1) afforded a pale yellow oil, which was treated with ethyl acetate. The resulting solid was collected by filtration and recrystallized from methanol to give 10.2 g (16.1%) of the aldehyde-acetal (XVI), colorless needles, mp 198—199°. IR ν_{max}^{Nujol} cm^{-1}: 3070, 1710, 1620, 1600. NMR ($CDCl_3$+d_6-DMSO) δ: 2.95 (3H, s, $OC\underline{H}_3$), 3.08 (3H, s, $OC\underline{H}_3$), 5.08 (1H, d–d, J_{AB}=13 Hz, J_{BX}=9 Hz, –CH_A=C<u>H</u>$_B$–CH_XO), 6.70—7.33 (4H, m, aromatic protons), 7.54 (1H, d, J_{AB}=13 Hz, –C<u>H</u>$_A$=CH_B), 9.04 (1H, d, J_{BX}=9 Hz, =CH_B–C<u>H</u>$_X$O), 10.57 (1H, s, N<u>H</u>). *Anal.* Calcd. for $C_{18}H_{22}O_4N_2$ (330.37): C, 65.44; H, 6.71; N, 8.48. Found: C, 65.30; H, 6.80; N, 8.35.

The filtrate was concentrated to dryness *in vacuo* to furnish 38.6 g (72.3%) of the amino-acetal (XV) as a pale yellow oil, which indicated one spot on TLC, though its NMR spectrum indicated two pairs of methyl proton signals of methoxy group, which suggested that the compound might consist of two 3-spiro isomers (XVa and XVb). IR ν_{max}^{Neat} cm^{-1}: 3220, 1705, 1620, 1600, NMR ($CDCl_3$) δ: 3.21 (s, $OC\underline{H}_3$), 3.27 (s, $OC\underline{H}_3$), 3.30 (s, $OC\underline{H}_3$), 3.36 (s, $OC\underline{H}_3$), 4.53 (1H, t, J=5 Hz, $C\underline{H}\langle^{OCH_3}_{OCH_3}$), 6.97—7.50 (4H, m, aromatic protons), 9.30 (1H, b-s, N<u>H</u>).

1′-(3-Oxobutyl)-2′-(2,2-dimethoxyethyl) Spiro[indoline-3,3′-pyrrolidine]-2-one (XVIIa,b)——To a solution of the amino-acetal [XVa, b, 38.5 g (0.15 mole)] in anhydrous benzene (500 ml) was added methyl vinyl ketone [17.6 g (0.255 mole)] with stirring in an ice bath, and the whole was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* to give 46.7 g (90.0%) of the keto-acetal (XVII) as a pale yellow oil, which indicated two spots on TLC and two pairs of methyl proton signals in its NMR spectrum, demonstrating the product to be a mixture of two 3-spiro isomers (XVIIa and XVIIb). The crude product was submitted to the subsequent reaction without purification. IR ν_{max}^{Neat} cm^{-1}: 3250, 1720, 1710, 1620, 1600. NMR ($CDCl_3$) δ: 2.30 (3H, s, $COC\underline{H}_3$), 2.97 (s, $OC\underline{H}_3$), 3.06 (s, $OC\underline{H}_3$), 3.09 (s, $OC\underline{H}_3$), 3.25 (s, $OC\underline{H}_3$), 6.93—7.49 (4H, m, aromatic protons), 9.65 (1H, s, N<u>H</u>).

6′-Acetyl-1′,2′,3′,5′,8′,8′a-hexahydro Spiro[indoline-3,1′-indolizine]-2-one (XIVa,b)——A mixture of the keto-acetal[XVIIa,b, 2.35 g (6.8 mmoles)], 10% hydrochloric acid (25 ml) and acetic acid (25 ml) was heated at 100° for 2 hr. After cooling, the reaction mixture was neutralized with 10% sodium carbonate solution and extracted with dichloromethane. The extract was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel. The first fraction eluted with ethyl acetate–ethanol (9: 1) afforded 0.52 g (31.0%) of the unsaturated ketone (XIVb), which was recrystallized from ethyl acetate to give the pure material, a pale yellow prisms, mp 144—145°. IR ν_{max}^{Nujol} cm^{-1}: 3240, 1705, 1695, 1665, 1640, 1620. NMR ($CDCl_3$) δ: 2.27 (3H, s, $COC\underline{H}_3$), 6.65—7.47 (5H, m, aromatic protons and an olefinic proton), 9.02 (1H, s, N<u>H</u>). Mass Spectrum *m/e*: 282 (M^+), 160, 137, 122 (base peak). *Anal.* Calcd. for $C_{17}H_{18}O_2N_2$ (282.33): C, 72.32; H, 6.43; N, 9.92. Found: C, 72.35; H, 6.46; N, 9.87.

The second fraction eluted with the same solvent gave 1.2 g (65.1%) of the unsaturated ketone (XIVa), which was recrystallized from methanol to furnish the pure material, pale yellow prisms, mp 171°. IR ν_{max}^{Nujol} cm^{-1}: 3060, 1715, 1700, 1665, 1640, 1620, NMR ($CDCl_3$) δ: 2.27 (3H, s, $COC\underline{H}_3$), 6.75—7.30 (5H, m, aromatic protons and an olefinic proton), 9.30 (1H, s, N<u>H</u>). Mass Spectrum *m/e*: 282 (M^+), 160, 137, 122 (base peak). *Anal.* Calcd. for $C_{17}H_{18}O_2N_2$ (282.33): C, 72.32; H, 6.43; N, 9.92. Found: C, 72.37; H, 6.46; N, 9.92.

6′,8′-Dioxo-9′-methoxycarbonyl-1′,2′,3′,5′,5′a,6′,7′,8′,9′,9′a,10′,10′a-dodecahydro Spiro{indoline-3,1′-pyrrolo[1,2-*b*]isoquinoline}-2-one (XIXa)——Dimethyl malonate [111 mg, (0.84 mmole)] in dry methanol (0.5 ml) was added to a methanolic solution of sodium methoxide prepared by dissolving sodium (18 mg, 0.77 mg-atom) in dry methanol (1 ml) in an ice-bath. To the mixture was added a solution of the unsaturated ketone

[XIVa, 197 mg (0.7 mmole)] in dry methanol (2 ml). The whole mixture was stirred at room temperature overnight and evaporated *in vacuo* to give the residue, to which was added a small amount of water. The solution was neutralized with 10% acetic acid and treated with ether. The resulting solid was collected, washed with a cold water, and dried to give 222 mg (83.0%) of the diketo-ester (XIXa), which was recrystallized from methanol to give the analytically pure material, colorless needles, mp 203—204° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3550—3200 (broad), 3170, 1725, 1720, 1620. NMR (d_6-DMSO) δ: 3.30 (3H, s, $CO_2C\underline{H}_3$), 6.72—7.42 (4H, m, aromatic protons), 10.21 (1H, s, N$\underline{H}$). Mass Spectrum *m/e*: 382 (M$^+$), 350, 237, 205, 159, 144. *Anal.* Calcd. for $C_{21}H_{22}O_5N_2 \cdot H_2O$ (400.42): C, 62.99; H, 6.04; N, 7.00. Found: C, 62.79; H, 6.12; N, 6.80.

6′-Acetyl-7′-bis (methoxycarbonyl) methyl Spiro [indoline-3,1′-indolizidine]-2-one (XXa)——Dimethyl malonate (2 ml) was added to a methanolic solution of sodium methoxide prepared by dissolving sodium [0.046 g (2 mg-atom)] in dry methanol (4 ml) under ice-cooling. To the mixture was added a solution of the unsaturated ketone [XIVa, 1.13 g (4 mmoles)] in dry methanol (10 ml). The whole mixture was stirred at room temperature overnight. The precipitate was collected by filtration and recrystallized from methanol to give 1.28 g (77.6%) of the keto-diester (XXa) as colorless needles, mp 204—205°. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1760, 1730, 1710, 1620. NMR (CF_3CO_2H) δ: 2.57 (3H, s, $COC\underline{H}_3$), 3.60 (3H, s, $COOC\underline{H}_3$), 3.92 (3H, s, $COOC\underline{H}_3$), 7.10—7.59 (4H, m, aromatic protons), 9.49 (1H, s, N$\underline{H}$). Mass Spectrum *m/e*: 414 (M$^+$), 383, 283, 279, 239, 226, 138 (base peak). *Anal.* Calcd. for $C_{22}H_{26}O_6N_2$ (414.44): C, 63.75; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.34; N, 6.71.

6′-Acetyl-7′-bis (methoxycarbonyl) methyl Spiro [indoline-3,1′-indolizidine]-2-one (XXb)——Dimethyl malonate (2 ml) was added to a methanolic solution of sodium methoxide prepared by dissolving sodium [0.046 g (2 mg-atom)] in dry methanol (4 ml) in an ice bath. To the solution was added a solution of the unsaturated ketone [XIVb, 1.13 g (4 mmoles)] in dry methanol (4 ml). After stirring at room temperature overnight, the reaction mixture was neutralized with 10% acetic acid and concentrated *in vacuo*. The residue was acidified with 10% hydrochloric acid, washed with ethyl ether several times, neutralized with saturated sodium bicarbonate under ice-cooling, and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure to leave 0.93 g (56.5%) of the keto-diester (XXb) as colorless powder, which showed a single spot on TLC. The crude material was recrystallized from ethyl ether to give the analytically pure material, colorless prisms, mp 171°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1745, 1715, 1695, 1620. NMR ($CDCl_3$) δ: 2.28 (3H, s, $COC\underline{H}_3$), 3.63 (3H, s, $COOC\underline{H}_3$), 3.70 (3H, s, $COOC\underline{H}_3$), 6.75—7.25 (4H, m, aromatic protons), 8.52 (1H, s, N$\underline{H}$). Mass Spectrum *m/e*: 414 (M$^+$), 383, 283, 279, 239, 226, 138 (base peak). *Anal.* Calcd. for $C_{22}H_{26}O_6N_2$ (414.44): C, 63.75; H, 6.32; N, 6.76. Found: C, 63.88; H, 6.38; N, 6.68.

6′-(1-Hydroxyethyl)-7′-bis(methoxycarbonyl)methyl Spiro [indoline-3,1′-indolizidine]-2-one (XXIb)——A solution of the keto-diester [XXb, 1.5 g (3.6 mmoles)] in methanol (50 ml) was hydrogenated on PtO_2 (0.15 g) for 48 hr at room temperature. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* and the residue was treated with ethyl ether. The resulting solid was collected by filtration to give 1.48 g (98.0%) of the hydroxydiester (XXIb), which showed a single spot on TLC and was recrystallized from ethyl acetate to afford the analytically pure material, colorless prisms, mp 181—182° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3200-(broad), 3080, 1735, 1720, 1620, NMR ($CDCl_3$) δ: 1.21 (3H, d, J=6 Hz $>$CH–C$\underline{H}_3$), 3.60 (3H, s, $COOC\underline{H}_3$), 3.69 (3H, s, $COOC\underline{H}_3$), 6.77—7.25 (4H, m, aromatic protons), 8.75 (1H, s, N$\underline{H}$). Mass Spectrum *m/e*: 416 (M$^+$), 384, 267, 249 (base peak), 194, 180. *Anal.* Calcd. for $C_{22}H_{28}O_6N_2$ (416.46): C, 63.44; H, 6.78; N, 6.73. Found: C, 63.33; H, 6.82; N, 6.62.

1′-β-Methyl-3′-oxo-3′,4′,4′a,5′,5′a,6′,7′,8′,10′,10′a-decahydro Spiro{indoline-3,6′-1′*H*-pyrano[3,4-*f*]indolizine}-2-one-(XXIIa,b)[27]——A solution of the hydroxy-diester [XXIb, 1.4 g (3.4 mmoles)] in acetic acid (30 ml), concentrated sulfuric acid (3.6 ml) and water (20 ml) was heated under reflux for 10 hr. The reaction mixture was concentrated *in vacuo* to leave the residue, which was neutralized with saturated sodium bicarbonate solution and extracted with dichloromethane. The extract was dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on silica gel. The first fraction eluted with ethyl acetate afforded 356 mg (32.1%) of the lactone (XXIIb), which was recrystallized from methanol–ethyl acetate to furnish the pure material, colorless prisms, mp 269° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1715, 1690, 1615. NMR (d_6-DMSO) δ: 1.24 (3H, d, J=6 Hz, C–1′–C$\underline{H}_3$), 4.14 (1H, m, C–1′–$\underline{H}$), 6.68—7.30 (4H, m, aromatic protons), 10.32 (1H, s, N$\underline{H}$). The multiplet of C–1′–H signal was collapsed to a doublet ($J_{1'-10'a}$=8 Hz) on irradiation at the C–1′–CH_3 frequency. Mass Spectrum *m/e*: 326 (M$^+$), 309, 267, 181 (base peak). *Anal.* Calcd. for $C_{19}H_{22}O_3N_2$ (326.38): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.77; H, 6.86; N, 8.48. The second fraction eluted with the same solvent gave 451 mg (40.6%) of the lactone (XXIIa), which was recrystallized from methanol–ethyl acetate to give colorless needles, mp 268° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1710, 1620. NMR (d_6–DMSO) δ: 1.24 (3H, d, J=6 Hz, C–1′–C$\underline{H}_3$), 4.10 (1H, m, C–1′–$\underline{H}$), 6.62—7.17 (4H, m, aromatic protons), 10.05 (1H, s, N$\underline{H}$). The multiplet of C–1′–H signal was collapsed to a doublet ($J_{1'-10'a}$=8 Hz) on irradiation at the C–1′–

27) The prefixes "α" and "β" in the formulas conventionally indicate the orientation of the C-1′-methyl substituent in each racemic compound which is delineated in one isomeric form, below and above the drawing plane, respectively.

CH_3 frequency. Mass Spectrum *m/e*: 326 (M^+), 309, 267, 181 (base peak). *Anal.* Calcd. for $C_{19}H_{22}O_3N_2$ (326.38): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.93; H, 6.81; N, 8.37.

6′-(1-Hydroxyethyl)-7′-bis(methoxycarbonyl)methyl Spiro[indoline-3,1′-indolizidine]-2-one (XXIVb)——To a solution of the keto-diester[XXb, 414 mg (1 mmole)] in methanol (5 ml) was added portionwise $NaBH_4$ [76 mg (2 mmoles)] at −5——10° and the mixture was stirred for 2 hr. The reaction mixture was diluted with ice-water and extracted with dichloromethane. The extract was dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was treated with ethyl ether and the resulting solid was collected by filtration to give 360 mg (86.9%) of the hydroxy-diester (XXIVb), which showed a single spot on TLC. The crude material was recrystallized from ethyl acetate to furnish the analytically pure material, mp 180—181° (decomp.), as colorless prisms. IR ν_{max}^{Nujol} cm^{-1}: 3200-(broad), 3080, 1740, 1720, 1620. NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6 Hz, >CH–C$\underline{H}_3$), 3.61 (3H, s, COOC$\underline{H}_3$), 3.69 (3H, s, COOC$\underline{H}_3$), 6.77—7.30 (4H, m, aromatic protons), 8.48 (1H, s, N$\underline{H}$). Mass Spectrum *m/e*: 416 (M^+), 384, 239. *Anal.* Calcd. for $C_{22}H_{28}O_6N_2$ (416.46): C, 63.44; H, 6.78; N, 6.73. Found: C, 63.08; H, 6.75; N, 6.53.

1′-α-Methyl-3′-oxo-3′,4′,4′a,5′,5′a,6′,7′,8′,10′,10′a-decahydro Spiro{indoline-3,6′-1′H-pyrano[3,4-*f*]indolizine}-2-one (XXVa,b)——A solution of the hydroxy-diester [XXIVb, 300 mg (0.72 mmole)] in acetic acid (10 ml), concentrated sulfuric acid (1.2 ml), and water (6.6 ml) was refluxed for 10 hr. After evaporation of the solvent the residue was neutralized with saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel. The first fraction eluted with a mixed solvent of ethyl acetate–methanol (9: 1) afforded 67 mg (28.6%) of the lactone (XXVb), which was recrystallized from methanol–ethyl acetate to give the pure material as colorless prisms, mp 258° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1715, 1690, 1615. NMR (d_6–DMSO) δ: 1.24 (3H, d, J=6 Hz, C–1′–C$\underline{H}_3$), 4.18 (1H, m, C–1′–$\underline{H}$), 6.76—7.25 (4H, m, aromatic protons), 10.35 (1H, s, N$\underline{H}$). The multiplet of C–1′–H signal was collapsed to a doublet ($J_{1'-10'a}$=4 Hz) on irradiation at the C–1′–CH_3 frequency. Mass Spectrum *m/e*: 326 (M^+), 309, 267, 181 (base peak). *Anal.* Calcd. for $C_{19}H_{22}O_3N_2$ (326.38): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.71; H, 6.83; N, 8.70. The second fraction eluted with the same solvent furnished 130 mg (55.6%) of the lactone (XXVa), which was recrystallized from methanol–ethyl acetate to give the analytically pure material, colorless needles, mp 254° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1710, 1690, 1620. NMR (d_6–DMSO) δ: 1.18 (3H, d, J=6 Hz, C–1′–C$\underline{H}_3$), 4.60 (1H, m, C–1′–$\underline{H}$), 6.66—7.20 (4H, m, aromatic protons) 10.05 (1H, s, N$\underline{H}$). The multiplet of C–1′–H singlet was collapsed to a doublet ($J_{1'-10'a}$=4 Hz) on irradiation at the C–1′–CH_3 frequency. Mass Spectrum *m/e*: 326 (M^+), 309, 267, 181 (base peak). *Anal.* Calcd. for $C_{19}H_{22}O_3N_2$ (326.38): C, 69.92; H, 6.79; N, 8.58. Found: C, 69.63; H, 6.90; N, 8.48.

1′-β-Methyl-3′-oxo-4′-dimethylaminomethylidene-3′,4′,4′a,5′,5′a,6′,7′,8′,10′,10′a-decahydro Spiro{indoline-3,6′-1′*H*-pyrano[3,4-*f*]indolizine}-2-one (XXVIa)——To a solution of the lactone [XXIIa, 130 mg (0.4 mmole)] in dimethylformamide (1 ml) was added freshly prepared bis-dimethylamino-*tert*-butyloxymethane-[226 mg (1.2 mmoles)]. The whole was heated at 50° for 1 hr and at 100° for further 1 hr. The reaction mixture was concentrated *in vacuo* to leave the residue, which was treated with water and extracted with dichloromethane. The extract was dried over Na_2SO_4 and evaporated under reduced pressure to give the residue, which was treated with ethyl ether. The resulting solid was collected by filtration and recrystallized from methanol–ethyl acetate to afford 110 mg (72.4%) of the vinylogous carbamate (XXVIa) as colorless needles, mp 254—255°. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1725, 1660, 1625, 1580. NMR (d_6–DMSO) δ: 1.18 (3H, d, J=6 Hz, C–1′–C$\underline{H}_3$), 3.30 (6H, s, $N\langle^{C\underline{H}_3}_{C\underline{H}_3}$), 6.72—7.35 (5H, m, aromatic protons+anolefinic proton), 10.14 (1H, s, N$\underline{H}$). Mass Spectrum *m/e*: 381 (M^+), 336, 191, 145 (base peak). *Anal.* Calcd. for $C_{22}H_{27}O_3N_3$ (381.46): C, 69.27; H, 7.13; N, 11.02. Found: C, 68.85; H, 7.11; N, 10.83.

1′-β-Methyl-3′-methoxy-3′,4′,4′a,5′,5′a,6′,7′,8′,10′,10′a-decahydro Spiro{indoline-3,6′-1′*H*-pyrano[3,4-*f*]-indolizine}-2-one (XXVIIa) and 1′-β-Methyl-3′-hydroxy-3′,4′,4′a,5′,5′a,6′,7′,8′,10′,10′a-decahydro Spiro{indoline-3,6′-1′*H*-pyrano[3,4-*f*]indolizine}-2-one (XXVIIIa)——A solution of the vinylogous carbamate [XXVIa, 100 mg (0.26 mmole)] in 10% hydrochloric acid (5 ml) was heated under reflux for 1 hr. The reaction mixture was concentrated *in vacuo* to leave the residue, to which was added 5% anhydrous methanolic hydrochloric acid (5 ml) and the whole was refluxed for 3 hr. After evaporation of solvent the residue was neutralized with saturated sodium bicarbonate solution and extracted with dichloromethane. The extract was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was subjected to preparative thin-layer chromatography (TLC) on silica gel using ethyl acetate–methanol (9: 1) as a developing solvent. The zone with *Rf* 6 gave 70 mg (78.9%) of the acetal (XXVIIa) as colorless crystals, mp 144—146° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1720, 1690, 1615. NMR ($CDCl_3$) δ: 1.12 (3H, d, J=6 Hz, C–1′–C$\underline{H}_3$), 3.28 (3H, s, OC$\underline{H}_3$), 4.62 (1H, m, C′$_3$–$\underline{H}$), 6.79—7.25 (4H, m, aromatic protons), 9.34 (1H, b–s, N$\underline{H}$). Mass Spectrum *m/e*: 342 (M^+), 311, 310, 267, 201, 197. *Anal.* Calcd. for $C_{20}H_{26}O_3N_2$ (342.42): C, 70.15; H, 7.65; N, 8.18. Found: C, 70.35; H, 8.13; N, 7.71. The zone with *Rf* 3 gave 2 mg of colorless crystals, and its mass spectrum indicated *m/e*: 328 (M^+), 310 (M^+–18), 279, 223, 206, 205, 183, 150, and 149 (base peak). Taking account of the above results the compound could be assigned for the hemiacetal (XXVIIIa).

1′-β-Methyl-3′-dimethylamino-4′-methoxycarbonyl-3′,4′,4′a,5′,5′a,6′,7′,8′,10′,10′a-decahydro Spiro{indoline-3,6′-1′*H*-pyrano[3,4-*f*]indolizine}2-one (XXIXa,b)——A solution of the vinylgous carbamate [XXVIa,

200 mg (0.6 mmole)] in 5% anhydrous methanolic hydrochloric acid (20 ml) was heated under reflux for 5 hr. The reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in water, neutralized with saturated sodium bicarbonate solution, and extracted with dichloromethane. The extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was subjected to preparative thin-layer chromatography (TLC) on silica gel using ethyl acetate–methanol (9: 1) as a developing solvent. The zone with *Rf* 7 gave 3 mg (1.4%) of the amino-ester (XXIXb) as colorless crystals, mp 223—224°, and its mass spectrum indicated *m/e* 413 (M^+), 368, 340, 267, 241, 223, 195, and 194, and also its fragmantation pattern was identical with those of the 3-spiro isomer (XXIXa) obtained below. Taking account of the above results the compound could be assigned for (XXIXb). The zone of *Rf* 6 afforded 198 mg (79.9%) of the amino-ester (XXIXa), which was recrystallized from dichloromethane-ethyl ether to give an analytical specimen, mp 228°, as colorless crystals. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1750, 1735, 1720, 1695, 1685, 1625. NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6 Hz, C-1′-C<u>H</u>$_3$), 2.32 [6H, s, N(C<u>H</u>$_3$)$_2$] 3.53 (3H, s, COOC<u>H</u>$_3$), 4.02 (1H, d, J=9 Hz, C-3′-<u>H</u>), 6.80—7.35 (4H, m, aromatic protons), 8.90 (1H, s, N<u>H</u>). Mass Spectrum *m/e*: 413 (M^+), 368, 340, 267, 241, 222, 195, 194. *Anal.* Calcd. for $C_{23}H_{31}O_4N_3$ (413.50): C, 66.80; H, 7.56; N, 10.16. Found: C, 66.89; H, 7.67; N, 9.99.

1′-β-Methyl-3′-hydroxy-4′-methoxycarbonyl-3′, 4′, 4′a, 5′, 5′a, 6′, 7′, 8′, 10′, 10′a-decahydro Spiro {indoline-3,6′-1′*H*-pyrano[3,4-*f*]indolizine}-2-one (XXXa,b), (±)-Formosanine (IIIa) and (±)-Isoformosanine (IIIb)——A mixture of the amino-ester dihydrochloride [XXIXa·2HCl, 117 mg (0.24 mmole)], dioxane (2 ml) and water (12 drops) was heated under reflux for 20 hr. The reaction mixture was evaporated *in vacuo* to leave the residue, which was neutralized with saturated sodium bicarbonate and extracted with dichloromethane. The extract was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was subjected to preparative thin-layer chromatography (TLC) on silica gel using ethyl acetate–methanol (9: 1) as a developing solvent. The zone of *Rf* 7 gave 11 mg (12.5%) of (±)-isoformosanine (IIIb), which was identical with the natural alkaloids on comparisons of the IR ($CHCl_3$) and mass spectrum, and *Rf* value on TLC. The detailed data were recorded below. The zone of *Rf* 6 gave 12 mg (13.6%) of (±)-formosanine (IIa), which was identified with the authentic specimens of the natural alkaloid on comparisons of the IR ($CHCl_3$) and mass spectrum, and *Rf* value on TLC. The detailed data were reported below. The zone of *Rf* 5 was afforded 20 mg (21.5%) of the hemiacetal-ester (XXXb), mp 150—153° (decomp.), as colorless crystals. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3280, 1720, 1705, 1620, 1600. NMR ($CDCl_3$) δ: 1.25 (3H, d, J=6 Hz, C-1′-C<u>H</u>$_3$), 3.60 (3H, s, COOC<u>H</u>$_3$), 4.82 (1H, d, J=8 Hz, C-3′-<u>H</u>), 6.77—7.40 (4H, m, aromatic protons), 8.41 (1H, b-s, N<u>H</u>). Mass Spectrum *m/e*: 386 (M^+), 369, 368, 354, 267, 241, 223, 209, 194. *Anal.* Calcd. for $C_{21}H_{26}O_5N_2$ (386.43): C, 65.27; H, 6.78; N, 7.25. Found: C, 65.15; H, 6.98; N, 7.01. The zone of *Rf* 4 gave 33 mg (35.5%) of the hemiacetal-ester (XXXa), mp 164—167° (decomp.), as colorless crystals. IR ν_{max}^{Nujol} cm^{-1}: 3440, 3250, 1720, 1705, 1620, 1600. NMR ($CDCl_3$) δ: 1.25 (3H, d, J=6 Hz, C-1′-C<u>H</u>$_3$), 3.60 (3H, s, COOC<u>H</u>$_3$), 4.80 (1H, d, J=8 Hz, C-3′-<u>H</u>), 6.82—7.24 (4H, m, aromatic protons), 8.50 (1H, b-s, N<u>H</u>). Mass Spectrum *m/e*: 386 (M^+), 369, 368, 354, 267, 241, 223, 209, 194. *Anal.* Calcd. for $C_{21}H_{26}O_5N_2$ (386.43): C, 65.27; H, 6.78; N, 7.25. Found: C, 64.88; H, 6.77; N, 6.90.

(±)-Formosanine (IIIa) and (±)-Isoformosanine (IIIb)——1) To a solution of the lactone [XXIIa, 125 mg (0.38 mmole)] in dimethylformamide (1 ml) was added freshly prepared bis-dimethylamino-*tert*-butyloxymethane [198 mg (1.14 mmoles)]. The whole was heated at 50° for 1 hr and at 100° for further 1 hr. The reaction mixture was concentrated under reduced pressure to leave the residue, which was treated with water and extracted with dichloromethane. The extract was dried over Na_2SO_4 and evaporated to dryness *in vacuo* To the residue was added 5% anhydrous methanolic hydrochloric acid (6 ml) and the mixture was stirred at room temperature for 18 hr. The whole was concentrated *in vacuo* to leave the residue, to which were added dioxane (2 ml) and water (12 drops). The solution was heated under reflux for 20 hr. After evaporation of solvent the residue was made alkaline with saturated sodium bicarbonate solution and extracted with dichloromethane. The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in 1,2-dimethoxyethane (3 ml) and polyphosphoric acid (3 drops) was added to this solution. The whole was heated with stirring at 70° for 2 hr. After evaporation of solvent the residue was treated with an ice-water, made alkaline with saturated sodium bicarbonate solution and extracted with dichloromethane. The extract was dried over Na_2SO_4 and concentrated *in vacuo* to leave the residue, which was subjected to preparative thin-layer chromatography (TLC) on silica gel using ethyl acetate–methanol (9: 1) as a developing solvent. The zone with *Rf* 7 gave 27 mg (19.3%) of (±)-isoformosanine (IIIb), mp 222—224°, as colorless crystals, which was identical with the natural alkaloid on comparisons of IR ($CHCl_3$), Mass Spectrum and *Rf* values on TLC. Recrystallization from ethyl ether–*n*-hexane afforded an analytical specimen, mp 225—226°, as colorless needles. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1710 (sh), 1695, 1680 (sh), 1610. NMR ($CDCl_3$) δ: 1.29 (3H, d, J=7 Hz, C-1′-C<u>H</u>$_3$), 3.51 (3H, s, COOC<u>H</u>$_3$), 3.75 (1H, m, C-1′-<u>H</u>), 6.78—7.44 (5H, m, aromatic protons and an olefinic proton), 8.06 (1H, s, N<u>H</u>). Mass Spectrum *m/e*: 368 (M^+), 351, 337, 223 (base peak), 208. *Anal.* Calcd. for $C_{21}H_{24}O_4N_2$ (368.42): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.43; H, 6.65; N, 7.39. The zone with *Rf* 5 afforded 49 mg (35.0%) of (±)-formosanine (IIIa), mp 225—226°, as colorless crystals, which was identified with the natural alkaloid on comparisons of IR ($CHCl_3$), Mass Spectrum and *Rf* values on TLC. Recrystallization from ethyl acetate gave the analytically pure material, mp 235—236°, as colorless needles. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1715 (sh), 1695, 1680 (sh), 1615. NMR ($CDCl_3$) δ: 1.24 (3H, d, J=7 Hz, C-1′-C<u>H</u>$_3$), 3.52 (3H, s, COOC<u>H</u>$_3$), 3.73 (1H, m, C-1′-<u>H</u>), 6.79—7.44 (5H, m, aromatic protons and an olefinic proton), 8.23

(1H, s, NH). Mass Spectrum *m/e*: 368 (M^+), 351, 337, 223 (base peak), 208. *Anal.* Calcd. for $C_{21}H_{24}O_4N_2$ (368.42): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.24; H, 6.60; N, 7.47.

2) To a solution of the hemiacetal-ester [XXXa, 7.7 mg (0.02 mmole)] in 1,2-dimethoxyethane was added polyphosphoric acid (2 drops) and the whole was heated with stirring at 70° for 2 hr. The reaction mixture was concentrated *in vacuo* to leave the residue, which was treated with an ice-water, made alkaline with saturated sodium carbonate solution and extracted with dichloromethane. The extract was dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue gave 7.4 mg of (±)-formosanine as colorless crystals, which was identified by comparing its IR ($CHCl_3$), mass spectrum and *Rf* values on TLC with those of the natural alkaloid.

(±)-Mitraphylline (IIa) and (±)-Isomitraphylline——A mixture of the lactone[XXVa, 125 mg (0.38 mmole)], bis-dimethylamino-*tert*-butyloxymethane[198 mg (1.14 mmoles)] and dimethylformamide (1 ml) was heated at 50° for 1 hr and at 100° for further 1 hr. The reaction mixture was concentrated *in vacuo*. The residue was treated with water and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. To the residue was added 5% anhydrous methanolic hydrochloric acid (6 ml). After stirring at room temperature for 18 hr, the whole mixture was concentrated to dryness *in vacuo*. The residue was dissolved in aqueous dioxane [dioxane (2 ml) and water (12 drops)], and then refluxed for 24 hr. After evaporation of solvent the residue was made alkaline with saturated sodium bicarbonate solution and extracted with dichloromethane. The extract was dried over Na_2SO_4 and evaporated *in vacuo* to leave the residue, which was dissolved in 1,2-dimethoxyethane (3 ml) and to this solution was added polyphospholic acid (3 drops). The mixture was heated with stirring for 2 hr and concentrated *in vacuo* to give the residue, which was treated with ice-water, made alkaline with saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer, after drying over Na_2SO_4 and evaporation, was subjected to preparative thin-layer chromatography (TLC) on silica gel using ethyl acetate–methanol (9: 1) as a developing solvent. The zone with *Rf* 7 gave 22 mg (15.7%) of (±)-isomitraphylline (IIb), mp 217—220°, as colorless crystals, which was identical with the natural alkaloid on comparisons of the IR ($CHCl_3$), mass spectrum and *Rf* values on TLC. Recrystallization from ethyl ether–*n*-hexane furnished an analytical specimen, 222—223°, as colorless needles. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1720 (sh), 1700, 1685 (sh), 1615. NMR ($CDCl_3$) δ: 1.13 (3H, d, J=7 Hz, C-1′-CH$_3$), 3.56 (3H, s, COOCH$_3$), 4.39 (1H, m, C-1′-H), 6.80—7.40 (5H, m, aromatic protons and an olefinic proton), 7.95 (1H, s, NH). Mass Spectrum *m/e*: 368 (M^+), 351, 337, 223 (base peak), 208. *Anal.* Calcd. for $C_{21}H_{24}O_4N_2$ (368.42): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.41; H, 6.68; N, 7.33. The zone with *Rf* 5 afforded 38 mg (27.1%) of (±)-mitraphylline (IIa), mp 223—224°, as colorless crystals, which was identified with the authentic specimen of the natural alkaloid on direct comparisons of the IR ($CHCl_3$), mass spectrum and *Rf* values on TLC. Recrystallization from ethyl acetate gave the analytically pure material, mp 242°, as colorless needles. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1720 (sh), 1705, 1685 (sh), 1620. NMR ($CDCl_3$) δ: 1.11 (3H, d, J=7 Hz, C-1′-CH$_3$), 3.58 (3H, s, COOCH$_3$), 4.34 (1H, m, C-1′-H), 6.80—7.40 (5H, m, aromatic protons and an olefinic proton), 8.36 (1H, s, NH). Mass Spectrum *m/e*: 368 (M^+), 351, 337, 223 (base peak), 208. *Anal.* Calcd. for $C_{21}H_{24}O_4N_2$ (368.42): C, 68.46; H, 6.57; N, 7.60. Found: C, 68.51; H, 6.63; N, 7.53.

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